Original Article

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Dapsone as an Alternative Therapy in Children with Familial Mediterranean Fever

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Abstract

Objective: Familial Mediterranan Fever is an hereditary autoinflammatory disease that presents with recurrent febrile attacks and poly serositis. Colchicine is the only known treatment in this diease. However, nearly 5-10% of patients are resistant to colchicines. There are many different modalities in colchicine resistant patients, biologic and immunosupressive drugs being the known ones. We studied the efficacy of Dapsone as an anti inflammatory drug in children with FMF who did not tolerate colchicine well.

Methods: This is a case series study in 10 patients who had FMF on the base of Tel-Hashomer criteria and did not tolerate colchicine or did not respond to it well. Patients took 2mg/kg dapsone in single dose, during 6 months.

Findings In four patients episodic attacks returned after 27 days, so the drug was discontinued. One patient refused to continue the study; in five patients dapsone was taken in average for 8 months and 6 days, at least for 6 months. These five patients had no episodes of attack during the following observation.

Conclusion: Dapsone could control episodic attacks of FMF in 50% of cases. It might be considered as an alternative therapy in FMF cases not responding to colchicine.

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Key Words: Dapsone; Familial Mediterranan Fever; Periodic Fever; Children

Introduction

Famlial mediterranean fever (FMF) is a genetic disease characterized by recurrent painful attacks of fever and polyserositis, usually peritonitis, pleuritis and arthritis. A typical attack can be prevented with regular daily administration of colchicine in the most patients[1]. However, about ten percent of patients do not respond to colchicine or are completely resistant to the drug[2]. There is no known alternative or adjunct to colchicine therapy, although non-steroidal anti-inflammatory drugs (NSAIDs) may be of some benefit for synovial symptoms[3]. Therapeutic options for this important group of patients are unsatisfactory as proposed agents have only been studied in individual cases or in small, nonrandomized trials. Nonetheless, patients suffering frequent or disabling attacks on a maximal tolerated dose of oral colchicine, may be offered a therapeutic trial with 1 mg weekly intravenous colchicine, in addition to the regular oral regime[4]. Alternatively, efficacy of TNF inhibitors has been shown in several case reports, with significant improvement in attack parameters for both etanercept and infliximab[5,6,7]. Thalidomide, an anti-inflammatory agent with anti-TNF properties, was also

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efficacious in a small group of patients[8]. IFN-α was successful in an open label trial[9].

Over the years, a myriad of cytokines, chemokines and other inflammation-associated proteins have been studied in FMF patients, the cytokine/chemokine pattern is consistent with nonspecific inflammation [2]. Chemotaxis and apoptosis and finaly inflammasome formation has main role in FMF inflammation[10].

The mechanism of colchicine in controling FMF attacks is not known clearly, the most important effect of prophylactic doses of colchicine is to prevent chemotaxis of neutrophils [11]. Morever the anti-apoptosis effect of colchine also has been shown [12].

Dapsone has been the principal drug in a multidrug regimen recommended by the World Health Organization for the treatment of leprosy [13]. As an anti-infective agent, it is also used for treating malaria [14] and for Pneumocystis carinii pneumonia in AIDS patients [15].

A considerable number of other inflammatory diseases (ITP and vasculitis) have been shown to respond in varying degrees to dapsone [16-21]. Dapsone stabilizes neutrophil lysosomes[22] Several studies showed that dapsone may impair neutrophil chemotaxis [23]. Dapsone suppressed integrin-mediated neutrophil adherence function. It also inhibited chemoattractant-induced signal transduction and thus suppressed neutrophil recruitment and local production of toxic products in the affected skin of neutrophilic dermatoses[24]. From the above, can be concluded that neutrophils and neutrophil products are the major targets for this drug.

We observed similar therapeutic effects of dapsone with colchicines. This observation led us to try dapsone in FMF patients who could not tolerate colchicine, and/or had side effects that encouraged them to discontinue the medication.

Subjects and Methods

This was a descriptive study conducted in FMF and periodic fever clinic in Ardabil University of Medical Sciences. We identified 10 children among FMF patients who fulfilled Tel-Hashomer diagnostic criteria for definite FMF. We do not use routinely MEFV gene analysis in our FMF clinic, it is limited to investigational and some doubtful cases[25,26]. None of patients had any symptoms suspicious of combined and/or associated disease with FMF, like JIA and vasculitis.

They were on regular colchicine treatment. All of the patients had GI discomfort and were intolerant to colchicine and showed some degree of tendency to refuse to continue drug taking. Including criteria were having FMF on the basis of Tel-Hashomer criteria, and any side effect of colchicine, especially GI symptoms.

The patients were informed about the possible benefits and potential side-effects of dapsone, and they accepted to take the drug at least for 6 months. Informed consent approved by the ethical committee of our institute (ARUMS) was obtained from each patient's parents.

One patient in this group disagreed to continue the study.

In all patients G6PD was checked before dapsone with 2mg/kg dosage was begun. Patients were observed closely for the side effects of dapsone, especially on GI, liver and hematological aspect.

Findings

Four patients had recurrent episodes like before colchicine therapy after a few weeks (in average 27 days) of dapsone medication, so discontinuing it they were excluded from the study. One patient refusesd to take the drug and five patients took dapsone for averagely 8 months and 6 days, at least for 6 months. These five patients did not have any episode during study. The patients' characteristics and result of treatment are summarized in Table 1.

Discussion

Chemotaxis, apoptosis and finally inflammasome formation has main role in FMF inflammation [10]. The most important effect of prophylactic doses of

Table 1: Characteristics of patients with Familial Mediterranean Fever and result of treatment with Dapsone

SEX	Age	Before colchicine			After colchicine					After dapsone				
		Period of attack	Duration	Severity	Age at onset of colchicine	Dosage of colchicine	Period of pain	Duration	Severity	Dosage of dapsone	Lengthy of dapsone therapy	Number of attacks	severity
M	6yr	7-10 days	72 - 96 hr	10	1. 5yr	0. 5mg BID	2 times in 4. 5 years	3 -4 hr	10	30 mg daily	3Mo & 17day	1time	10 10
F	8yr	2 days	1 -2 hr	10	3. 5yr	0. 5mg BID	2-3 times in month	0. 5 – 1 hr	7	50mg daily	3Mo & 17day	1time	10
F	5yr	At first : 30 days Then: 3-8 days	o. 5 – 24 hr	10	1. 5yr	0. 5mg BID	NO	NO	NO	25mg daily	7 day	1time	10 10
F	7yr	Variable	3 -12 hr	9	2yr	0. 5mg daily	NO	NO	NO	50mg daily	14 day	2times	10 10
M	6yr	7 days	24 hr	7 - 8	2yr	0. 5mg daily	2 times in 4 years	12 hr	7 - 8	30 mg daily	< 7 day	NO	NO
M	10yr	20 -30 days	24 hr	9	4yr	0. 5mg BID	NO	NO	NO	50mg daily	9 Mo	NO	NO NO
F	7yr	15 – 20 days	3 -4 hr	10	5yr	0. 5mg daily	2 – 3 / month	72 hr	3	50mg daily	10 Mo	NO	NO
F	7yr	14 days	More than 96 hr	10	4yr	0. 5mg BID	NO	NO	NO	50mg daily	6Mo & 8 day	NO	NO
M	8yr	14 days	48hr	10	6yr	0. 5mg daily	2 times in 2 years	48 – 72 hr	5 - 6	50mg daily	9Mo	NO	NO
F	9yr	7 days	8 -9 hr	6	2yr	0. 5mg BID	No / pain Fever occasionally	NO	NO	50mg daily	9Mo	No attack*	NO

* but some febrile attacks without abdominal pain
M: Male / F: Female

colchicine is to prevent chemotaxis of neutrophils [11]. Moreover the anti-apoptosis effect of colchine also has been shown [12]. In this study we used dapsone in FMF children. Dapsone is an old and famous antibacterial drug, but it has some anti inflammatory effect [22-24], in some aspects these effects are similar to the colchicine effect in FMF. Dapsone inhibits beta2 integrin (CD11b/CD18)-mediated adherence of human neutrophils, interferes with the activation or function of the G-protein (Gi type) that initiates the signal transduction cascade common to chemo- tactic stimuli, inhibits the generation of second messengers essential to the activation of beta2 integrin molecules as well as respiratory and secretory functions of neutrophils exposed to chemo attractants [24]. In five patients we did not see FMF attacks during at least six months (mean, 8 months and 6 days) of observation. Certainly it relates to anti-inflammatory effect of dapsone, which, compared with colchicine efficacy of 80%[1], is not very high, but having 50% response, and because of similar action on immune response, it may be useful as an alternative therapy in some, especially colchicine resistant patients. We did not see any side effects of dapsone, and it has been well tolerated in children. MEFV gene analysis in these patients may be helpful and may give more information about the mutations which respond to dapsone, although it was not the scope of our study.

In the review of literature we did not find a similar study, and to our best knowledge, this seems to be the first experience on dapsone treatment of FMF particularly in children.

A limitation of this study is the lack of MEFV gene analysis. Another limitation is the short duration of the study caused by lack of long-term availability of the drug.

Conclusion

It seems that dapsone might be considered as an alternative therapy in FMF non- responding to colchicine patients.

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Conflict of Interest: There is no any conflict of interest in this study and publishing of it.

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